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M Potegal, M Hebert, M DeCoster, JL Meyerhoff

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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Walter Reed Army Institute of Research
Washington, DC 20307-5100

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Brief 200 Hz stimulation of the corticomedial amygdala increases the aggressiveness of male Syrian golden hamsters for a period of about 30 min; the effect peaks 10-15 min after stimulation. This effect is sensitive to both current level and, unexpectedly, stimulation frequency. Stimulation at the same parameters that reduce attack latency increases flank marking but has no effect on general activity or on the latency to copulate with a female. Immunocytochemical analysis suggests that stimulation effects may be coupled to c-fos expression and that unilateral stimulation has bilateral effects. The aggression-facilitating effects of CMZ stimulation appear to mimic part of the time course of behaviorally induced attack priming. These findings suggest that the temporal persistence of aggression may result from LTP-like changes within neural circuitry of which the CMA is a part.

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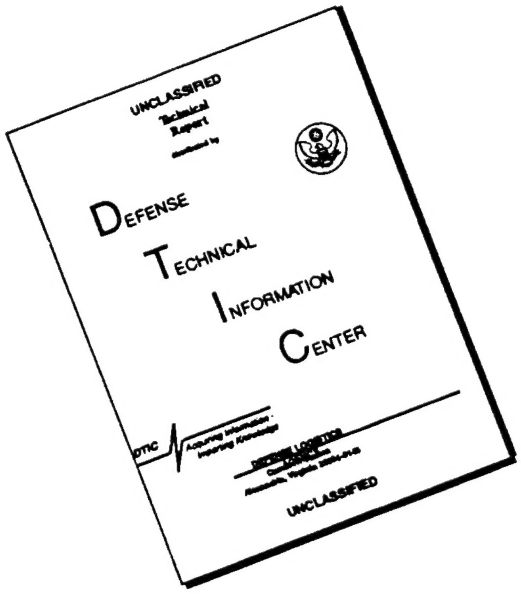

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Behavioral Neuroscience
1996, Vol. 110, No. 2, 401–412

Brief, High-Frequency Stimulation of the Corticomedial Amygdala Induces a Delayed and Prolonged Increase of Aggressiveness in Male Syrian Golden Hamsters

M. Potegal, M. Hebert, M. DeCoster, and J. L. Meyerhoff
Walter Reed Army Institute of Research

Brief 200-Hz stimulation of the corticomedial amygdala (CMA) increases the aggressiveness of male Syrian golden hamsters for about 30 min; the effect peaks 10–15 min after stimulation. This effect is sensitive to stimulation amplitude and frequency. Stimulation at the parameters that reduce attack latency increases flank marking but does not affect copulation latency or general activity. Immunocytochemical analysis suggests that stimulation effects may be coupled to *c-fos* expression and that unilateral stimulation has bilateral effects. CMA stimulation effects appear to mimic part of the time course of behaviorally induced attack priming. The temporal persistence of aggression may result from long-term potentiation-like changes within CMA-related neural circuitry.

Once sufficiently aroused, aggressive behavior in various species of fish (e.g., Heiligenberg, 1974), birds (e.g., Curio, 1975), and mammals (e.g., Potegal, 1992) tends to persist in time. Under experimental circumstances in which the aggression-provoking stimulus remains constant, temporal fluctuations in aggressive behavior imply the existence of fluctuations in central control processes. When aggression persists even after the provoking stimulus is withdrawn (e.g., Curio, 1975; Heiligenberg, 1974), such central processes must certainly play a role. We believe that these important but poorly understood internal processes contribute to a variety of phenomena within the domain of aggressive behavior and that any theory of aggression that fails to take them into account must remain incomplete (Potegal, 1994). Accordingly, we have developed an experimental model for the analysis of these processes based on the standard resident–intruder paradigm used in the study of rodent agonistic behavior. Priming a resident hamster or rat by allowing it to attack a conspecific intruder introduced into its home cage increases its aggressive arousal (i.e., decreases the latency and increases the probability of attack on a second intruder; Potegal, 1992; Potegal & Popken, 1985; Potegal & tenBrink, 1984). The demonstrated failure of the hamsters to discriminate one intruder from another (Potegal, 1991) is prima facie evidence that the change in latency from the first (priming) trial to the second (probe) trial must be internally mediated. Behavioral characterization of attack priming has ruled out some alternative interpretations, including the possibility that it induces a purely nonspecific arousal. Behaviors remaining unaffected by attack priming include wheel running, feeding (tested in females, Potegal & tenBrink, 1984), and copulation (tested in males, Potegal, Hebert, & Meyerhoff, 1996). Further evidence for central mediation arises from studies in which delays of various durations were interpolated between priming and probe trials: Attack latencies remain reduced for at least 30 min following priming (Potegal, 1992). The complex time course of behavioral attack priming in both female hamsters and male rats can be modeled by the addition of two processes. The first inferred process is maximal immediately after the priming attack and decays away with a half life on the order of several minutes. The second inferred process grows slowly, is high at about 30 min, and declines slowly after that.

Where and how in the central nervous system might these processes be mediated? Physiological studies have tended to treat aggression as a stimulus-bound reaction and, with the exception of one study in cats (Sledjeski & Flynn, 1972) and another in rats (Kruk, Meelis, Van der Poel, & Mos, 1981), have paid relatively little direct attention to the issue of temporal persistence. However, there are incidental but consistent observations in older studies of brain-stimulated aggression in cats and monkeys that the autonomic and behavioral signs of aggression occur more frequently and last longer (as long as 2–3 min) following the offset of amygdala stimulation than following offset of stimulation in either hypothalamus or

M. Potegal, M. Hebert, M. DeCoster, and J. L. Meyerhoff, Department of Medical Neurosciences, Walter Reed Army Institute of Research, Washington, DC.

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The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense (Para 4-3, AR 360-5). Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals, and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals* (NIH Publication 85-23). A preliminary report of this study was presented at the meeting of the Society for Neuroscience, October, 1992.

Correspondence concerning this article should be addressed to M. Potegal, who is now at the Psychology Department, W. J. Brogden Building, University of Wisconsin, 1202 W. Johnson Street, Madison, Wisconsin 53706. Electronic mail may be sent to Potegal@psyphy.psych.wisc.edu.

central gray (Allikmets, 1966; Gastaut, Vigoroux, Corriol, & Badier, 1951; Gunne & Lewander, 1966; Hilton & Zbrozyna, 1963; MacLean & Delgado, 1953; Rubinstein & Delgado, 1963). More recently, Adamec (1990) has reported that stimulation of the amygdalas of cats using trains of 15 pulses at 300 and 400 Hz produces electrophysiological changes in the amygdalo–VMH pathway associated with the cats' avoidance and escape from rats and increases in their predatory biting for periods greater than 45 min but less than 24 hr. Conversely, amygdala lesions reduced the duration of intraspecific fighting in dogs (Fuller, Rosvold, & Pribram, 1957) and postshock fighting in hamsters (Shipley & Kolb, 1977).

In rodents, lesion studies have implicated the medial and cortical nuclei of the amygdala (CMA) in offensive aggression (for hamsters, see Bunnell, Sodetz, & Shalloway, 1970; Potegal, Ferris, & Skaredoff, 1991; Potegal, Ferris, Hebert, Meyerhoff, & Skaredoff, in press; Shipley & Kolb, 1977; Takahashi & Gladstone, 1988; for rats, see Luiten, Koolhaas, Boer, & de Koopmans, 1985; Vochteloo & Koolhaas, 1987; for mice, Kemble, 1981). Conversely, in two studies reporting a lack of effect of amygdala lesions on intraspecific aggression in rats, the lesions were located mostly in the central and/or basolateral nuclei, or both (Blanchard & Takahashi, 1988; Busch & Barfield, 1974). Our recent findings, that attack primed hamsters show a behaviorally specific and neuroanatomically localized expression of the early intermediate gene *c-fos* in the CMA, directly link these structures to the temporal persistence of aggressive arousal (Potegal et al., 1991, in press). If the CMA is part of the circuitry mediating prolonged aggressive arousal, as the foregoing observations suggest, it follows that stimulation of these nuclei might produce a facilitation of aggression that persists over time. The present series of experiments was designed to explore the hypothesis that CMA stimulation would induce an extended reduction of attack latency. Electrical stimulation was chosen in preference to intracerebral drug injection in order to obtain precise control over the onset and offset of stimulation. Our preliminary observations indicated that the long pulse trains and high-duty cycles of 50-Hz stimulation typically used in studies of brain-stimulated behavior failed to facilitate subsequent attack. Taking as a possible model the physiological and behavioral effects of long-term potentiation of the amygdala (Henke, 1990; Uno & Ozawa, 1991; Racine, Milgram, & Hafner, 1983), we switched to shorter pulse trains of higher frequency stimulation at longer intervals. As we now report, the predicted reduction in hamsters' latencies to attack a subsequently presented conspecific intruder was observed using these parameters.

An important question is whether the *c-fos* coupled behavioral attack priming that we studied previously and the electrical attack priming described in this report operate through the same mechanisms. If so, one would expect to see increases in *c-fos* expression associated with stimulation that facilitated aggression. We therefore examined the effects of stimulation on the expression of *c-fos* in the brains of implanted animals.

General Method and Materials

Resident Subjects and Conspecific Intruders

Subjects were mature, 115–180-g male golden hamsters from SASCO (Small Animal Supply, Omaha, NE), which were individually housed in hanging polycarbonate cages with a woodchip bedding. Food and water were available ad lib except during testing. No sooner than a week after isolation, subjects were screened for aggressiveness by having a methotrimeprazine-treated conspecific intruder placed in their home cages for 10 min. All subjects selected for these studies attacked the intruder at least once (see Aggression Testing section below for the definition of attack). Data presented in this article are based on a pool of 58 hamsters, each of which was tested at least once following brain stimulation and once following a control manipulation, as described below.

Intruders were group-housed, 60–110-g male hamsters from the same supplier. These animals were routinely injected before use with the long-acting analgesic sedative methotrimeprazine (Levoprome, Lederle, 2–4 mg/kg i.m.), which reduces the stress of being attacked by raising pain thresholds. The drug also eliminates the wild flight that some intruders show after being attacked. Treated animals continue to locomote, however. Methotrimeprazine thus induces behavior that is adequate for the elicitation of aggression, is reasonably stable from trial to trial, and is consistent across intruders (Potegal, 1991). The validity and reliability of these intruders as elicitors of intraspecific aggression have been demonstrated in our previous studies (Potegal, Blau, Black, & Glusman, 1980; Potegal & tenBrink, 1984). The females used for copulation testing in Experiment 6 were ovariectomized under asceptic conditions no sooner than 2 weeks after their arrival at the laboratory. They were used for testing no sooner than 3 weeks after their surgery. All of the hamsters were maintained under a reversed 10:14-hr dark–light cycle.

Apparatus and Procedures

Electrode implantation. The bipolar electrodes were constructed by twisting Teflon-coated 0.13-mm dia stainless steel wire (316-5T, Medwire, Mt. Vernon, NY). The wires were cut to an overall length of 8.5 mm but trimmed at an angle to create a tip separation of 0.1–0.25 mm along the dorsoventral axis. Aseptic surgical techniques were used to implant a unilateral electrode under surgical depth Na thiopental anesthesia (Pentothal, Abbott, 100 mg/kg ip); supplements were given as necessary to maintain anesthesia. A warming pad maintained body temperature at 37 °C. The skull was first prepared with an acidulated fluoride solution to increase its hardness (Yamamoto & Kutscher, 1981). Self-tapping stainless steel screws, 00 size × 3.2 mm long, were threaded into the thick temporal ridges of the skull as anchors for the electrode mount. The electrode was stereotaxically lowered through a burr hole drilled 2.7-mm lateral to the skull midline at bregma. A third lead connected to a skull screw acted as reference for recording. After a thin layer of cyanoacrylate adhesive was applied to the skull, a mound of dental acrylic was built up around the electrode and screws.

Aggression testing. All of the testing was carried out in the subject's home cage, which was inserted without a cover into a close-fitting transparent Plexiglas stimulation chamber. A 1-cm overhang in the upper chamber walls fit over the rim of the cage, preventing subjects from climbing on the rim. The 38-cm high walls of this chamber prevented subjects' escape by jumping. Before each test, the subject was held by the experimenter while a cable from a commutator (#CAY-375-6, Airflyte, Bayonne, NJ) fixed above the test chamber was connected to its electrode socket. Four days after surgery, we began 3 days of habituation to this handling and cable connection procedure.

Aggression testing began no sooner than 1 week after surgery. Subjects were tested no more frequently than 1 per day. The aggression test on the 1st day always consisted of a control (nonstimulated) cable coupling and uncoupling followed by placement of a methotrimeprazine-treated intruder into a corner of the cage at the maximum possible distance from the subject. The intruder remained in the cage for 10 min or until it was attacked; if attacked, the intruder was withdrawn immediately afterward. As in our previous studies (e.g., Potegal & Coombes, 1995), an attack was scored when a subject performed a species-typical bite-and-kick movement or when the intruder squealed and struggled, or both, during physical contact with the subject.

Total time elapsing from the introduction of the intruder to the attack by the subject was recorded, as was the time the subject spent in contact with or within one half of a body length of the intruder. The latter measure of attack latency, the duration of contact–proximity prior to attack, generally amounts to 50–75% of total elapsed time. Prior studies have clearly shown that it yields a better indicator of attack priming effects than does total elapsed time (Potegal & Coombes, 1995), presumably because it is during contact and close proximity that the subject is most directly exposed to olfactory–vomeronasal cues from the intruder. Thus, all attack latencies reported here are contact/proximity durations prior to attack. Note that this measure, like conventional latency measures, is completely independent of what either hamster happened to be doing during the periods of contact and close proximity. An alternative way of describing this measure is that it is conventional elapsed-time latency minus the time the hamsters spent apart.

Brain-stimulation parameters and pretesting. Current from a two-channel Grass S88 stimulator (Quincy, MA) was passed through Grass SIU5B stimulus isolation units and delivered to the subject through a circuit containing a 100-kΩ current-limiting resistor in series with the subject; current was routinely monitored on an oscilloscope in parallel with the resistor. Stimulation consisted of brief trains of biphasic rectangular current pulses. Pilot studies indicated that aggression was optimally facilitated using a 0.1-ms pulse duration, a 100-ms train duration, and a 10-s intertrain interval; these parameters were used in all of the experiments to be reported here. In most experiments, four trains of stimulation were used (the exception in Experiment 1 is noted); thus, the inclusive period of stimulation in these experiments was 30 s. After current was passed, the cable was disconnected and a methotrimeprazine-treated intruder was presented. Control tests without stimulation had the identical format, including a 30-s cable connection, but no current was passed.

The effectiveness of a given set of stimulation parameters in reducing attack latencies was evaluated for each animal by calculating a stimulation index (SI) from a pair of trials with and without stimulation.

$$SI = \frac{\text{latency without stim} - \text{latency with stimulation}}{\text{latency without stim} + \text{latency with stimulation}}$$

Values of SI range from 1.0 (maximum facilitation of aggression) through 0.0 (no effect of stimulation) to −1.0 (maximum inhibition of aggression). Pilot studies had shown that there was often a marked difference in effects in a given hamster, depending on which electrode tip was used as the leading pulse cathode (sensitivity to cathode choice has been reported in other brain-stimulation studies; Bodnar, Steiner, Brutus, Ippolito, & Ellman, 1978; Steiner et al., 1978). We therefore determined which tip was the more effective cathode for each hamster using a pulse amplitude of 100 μA. For the experiments reported here, we selected the polarity configuration yielding the higher SI. If neither configuration produced a substantial reduction in attack latency (i.e., SI < 0.15), we then tried the two polarity configurations at 125 μA on the next test days. Subjects showing an attack latency reduction at 100 or 125 μA with at least one polarity configuration were used in the experiments reported here. The combination of current level and polarity yielding the greatest reduction in attack latency in a given subject are referred to as that subject's optimal parameters. Some hamsters participated in more than one experiment. Baseline attack latencies (i.e., latencies following cable connection control) were determined anew for each experiment. Locations of the electrode tips in subjects not showing a reduction in attack latency and therefore not used in further testing are included in Figure 2.

Electrographic recording. In some cases, the poststimulation aggression test was omitted, and instead electrographic activity was recorded from the amygdala electrode just before and a few seconds after stimulation. This was accomplished using a double-pole, three-position switch that directed the signal from the electrodes to a Grass 7P511J preamplifier writing out to a 79D Polygraph.

Histology and Fos immunocytochemistry Labeling of Fos immunoreactive nuclei was carried out on brain sections from 11 hamsters with positive SI values, killed following stimulation, and 8 hamsters that had only a cable connection control (all other brains were just stained with toluidine blue after cutting). No testing was done between manipulation and overdosing. One hour after the manipulation, hamsters were killed by Na pentobarbital overdose (Nembutal, 250 mg/kg ip). Cardiac perfusion with 100-ml heparinzed saline delivered by peristaltic pump was followed by 100 ml of 4% paraformaldehyde in 0.1-M phosphate buffered saline (PBS, pH 7.4). Brains were postfixed in paraformaldehyde for 1 hr and transfered to 30% sucrose in PBS. No sooner than 24 hr later, they were cut at 50 μ on a freezing microtome. A 15-min incubation in 0.3% H_2O_2 to eliminate endogenous peroxidases was followed by a 30-min incubation in 10% normal goat serum (NGS) in PBS, with 0.2% Triton X at 4 °C and then a 15-min incubation in 2% NGS at room temperature. Overnight incubation in 0.2-μg/ml primary Fos antibody (i.e., 1:500 dilution of rabbit polyclonal antibody Aβ-2; Oncogene Science, Manhassett, NY) was carried out in 2% NGS and 0.1% bovine serum albumin at 4 °C. The secondary antibody was 1-μg/ml biotinylated goat antirabbit IgG (Vector Laboratories, Burlingame, CA). The tertiary layer, an avidin/biotinylated horseradish peroxidase H complex, was added with a Vectastain *Elite* ABC Kit (Vector Laboratories, Burlingame, CA), following manufacturer's instructions. After conditioning in 0.1-M acetate buffer, the sections were exposed to a solution containing 0.025% prefiltered diaminobenzidine tetrahydrochloride as the primary chromagen and 2.5% $NiNH_2SO_4$ as an enhancer (Hancock, 1986); H_2O_2 was added to produce a 0.0125% solution just before exposure. A group of randomly chosen sections was monitored under a dissecting microscope until the nuclei became visible (usually 3–5 min), at which point the reaction in all sections was terminated by immersion in 0.1-M acetate buffer. Tests for specificity were (a) omission of the primary antibody, (b) substitution of normal rabbit IgG for the primary, and (c) preadsorption of the primary antibody with 1.0-μg/ml Fos protein (Oncogene Science, Manhassett, NY).

All of the tests eliminated nuclear staining. Brains were routinely counterstained with toluidine blue. To ensure comparability of measurement across different hamsters, bilateral counts were taken at four coronal levels of the amygdala defined by the following white matter landmarks shown in Figure 2 (AL = amygdala level): AL1, The caudal margin of the optic chiasm (some optic chiasm fibers still visible across the ventral surface of the hypothalamus but the optic tract is assuming its characteristic triangular shape at the medial edge of the temporal lobe); AL2, where a line drawn through the middle of the fornices bisected the optic tract dorsoventrally; AL3, where a line through the fornices coincided with the medial edge of the optic tract; and AL4,

where the ventral edges of the cerebral peduncle and the optic tract coincided. These levels are roughly 350 μm apart.

Working at 100×, using the INSIGHT digitized video image system and IQ software (Meridian Systems, Okemos, MI), counts of the medial nucleus at all levels included all stained nuclei within a 0.148-mm^2 sampling circle positioned tangent to the ventral edge of the temporal lobe. The offset from the ventrolateral edge of the optic tract to the center of the sampling circle was predetermined for each AP level in pilot studies in order to sample within the densest concentration of medial nucleus neurons. The contrast for each image to be digitized and counted was adjusted so that a visually identified group of nuclei within the counting field was well imaged. Counters were unaware whether or not the brain had been stimulated before overdosing.

Experiment 1: CMA Stimulation Frequency-Attack Latency Function

Method

Behavioral studies of long-term potentiation (LTP) have used frequencies within the range of 62–400 Hz, typically with little indication of why a particular frequency was selected. As a methodological issue, we determined if there was an optimal frequency for effects on aggression. For the initial determination of the stimulation frequency-attack latency function 7 subjects were stimulated at frequencies of 40, 100, 200, and 400 Hz in counterbalanced order. Each subject was stimulated with two, four, or eight trains at every frequency; the number of trains selected for a given subject was that which reduced its attack latency to a minimum in a pilot study. Train duration was varied reciprocally with frequency so that the number of pulses was fixed at 30 pulses per train. In other words, a given subject received the same number of pulses at every stimulation frequency; the total number of pulses per test varied from 60 to 240 for different hamsters. The stimulation–test interval was 30 s.

Shortly after carrying out these tests, we completed a pilot study on the time course of electrical priming, which suggested that facilitation of attack might be maximal 10 min after the stimulation. We incorporated this information into a replication of the frequency-attack latency function in a group of 6 different subjects that were stimulated at 100, 200, and 400 Hz in counterbalanced order. In this replication, all subjects received four stimulation trains, with 20 impulses per train and a stimulation–test interval of 10 min. Pulse amplitude was 100 μA in every test.

Results

Stimulation frequency proved to be a surprisingly crucial parameter in obtaining the predicted electrical priming effect. As shown by the lower of the two frequency-attack latency functions in Figure 1, a striking reduction in attack latencies following 200-Hz stimulation was found, using an individually predetermined number of trains for each subject, 30 impulses per train, and a stimulation–test interval of 30 s. At this frequency, every subject attacked in less than 22 s. As the upper curve of Figure 1A shows, this frequency-tuning effect was then replicated using four stimulation trains for each subject, 20 impulses per train, and a stimulation–test interval of 10 min. The combined differences in log-transformed attack latency as a function of stimulation frequency are statistically significant, $F(3, 33) = 4.6, p < .01$.

Experiment 2: Time Course of CMA Stimulation Effects on Attack Latency

Method

The original pilot study of time course suggested that CMA stimulation induces a delayed and prolonged reduction in attack latency. It also revealed great variability among subjects. Having established the optimal stimulation frequency, we returned to the study of time course. Using 10 new subjects, we interpolated counterbalanced intervals of 1, 10, 30, and 90 min between stimulation and testing. In this experiment, we relinquished the initial tests to establish polarity and current level because of the bias introduced by testing at one given interval. Instead, we fixed current level at 100 μA and tested

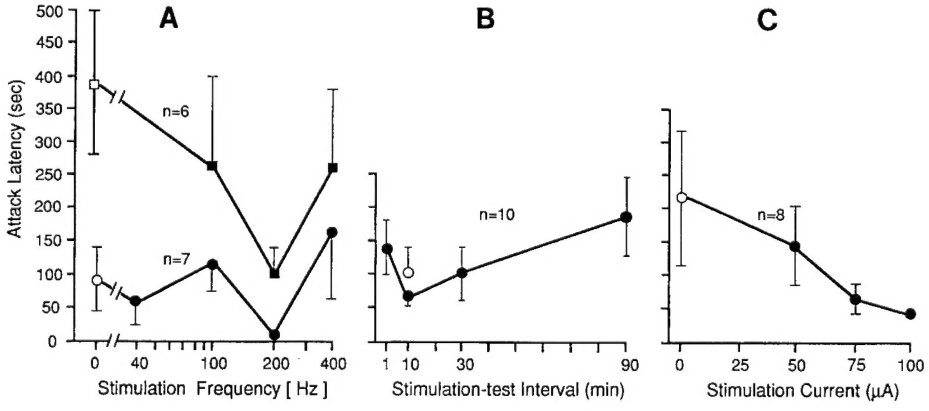

Figure 1. A: Mean attack latency as a function of stimulation frequency. Filled squares represent effects of four trains of stimulation with 20 impulses per train and a stimulation–test interval of 10 min. Filled circles represent effects of 30 impulses per train and a stimulation–test interval of 30 s. B: Mean attack latency as a function of the stimulation–test interval. C: Mean attack latency as a function of stimulation current. In all panels, the number of subjects used in each experiment is noted on the figure. Filled symbols represent tests following stimulation; open symbols represent tests following cable connection control. Error bars are SEMs.

all of the subjects at all four intervals, using first one and then the other electrode tip as cathode. We selected for the main analysis data from the polarity configuration for each hamster that yielded the shortest mean latency across the four intervals. On days prior to and following this testing, each subject was also given a control, nonstimulated test 10 min after a cable connection control.

Results

Latency data for 1 subject were collected from only one polarity configuration. These data were included with the set of latencies defined by the shortest mean value collected from each of the 9 other subjects. (This was a conservative decision, inasmuch as, if this polarity configuration yielded what would have been the higher rather than the lower set of latencies for this subject, the inclusion of this subject's data would have worked against the effect reported below.) A U-shaped interval–latency function was the modal response pattern, being generated by 6 of the 10 subjects (the probability of a strict U pattern arising by chance is 0.23, assuming for simplicity that no latency values on a 4-point curve can be exactly equal in value). As shown in Figure 1B, the overall interval–mean attack-latency function was also U-shaped, reaching a nadir 10 min after stimulation. This reduction in latency is still evident 20 min later, $F(3, 27) = 3.2$, $p < .04$. The shorter of the two latencies observed 10 min after stimulation was significantly less than the shorter of the two attack latencies observed 10 min after cable connection control (i.e., stimulation with this delay reduced attack latency below control levels), $t(9) = 2.99$, $p < .02$. A significant effect of stimulation–test interval was also found when the mean latencies from the two polarity configurations were used, $F(3, 27) = 3.5$, $p < .03$. Similarly, the mean latency on the two trials given 10 min after stimulation was significantly less than the mean latency on the two trials 10 min after the cable connection control, $t(9) = 2.3$, $p < .05$. As expected from our earlier finding of a preferred polarity configuration, however, there was no significant effect of stimulation–test interval when only the data from the configuration with the longer mean latency were evaluated, $F(3, 27) = 2.3$, and there was no difference between the longer stimulated and nonstimulated latencies at the 10-min stimulation–test interval, $t(9) = 1.8$.

A possible confound in these results is that even after 3 days of habituation to being held while the stimulation cable was connected, subjects might still have been stressed by this procedure. Thus, the changes in attack latencies with time since stimulation could merely reflect the recovery from the stress of handling. This hypothesis was tested with another group of 10 implanted subjects that were handled in the course of having the cable connected to their electrode socket for 30 s but were not stimulated (the cable connection control). These hamsters were tested with the same four intervals in counterbalanced order. Only 3 of these subjects showed a U-shaped, interval–latency function (the number expected by chance is 2.3). There was no systematic relationship between attack latency and the interval interpolated between cable connection and test in this group, $F(3, 27) = 0.41$.

Experiment 3: CMA Stimulation Current-Attack Latency Function

Method

Experiments 1 and 2 supported the existence of an electrical attack priming effect, but they are relatively complicated parametric studies in which there were no obvious a priori quantitative expectations to which empirical results could be compared. For a more straightforward demonstration of the effects of CMA stimulation, we next varied the current systematically from 0 to 100 μA. The recommended ($1/r^2$) approximation of current density–distance relations (Bagshaw & Evans, 1976; Yeomans, 1990) implies that progressively larger volumes of tissue will be stimulated as current increases. If the CMA operates in a mass action mode (i.e., the more neurons that are activated, the greater the aggressive arousal), then it is reasonable to expect that attack latency might be inversely related to current level. Qualitatively, this procedure can be thought of as the electrical equivalent of the classic dose–effect function in pharmacology. Using 200-Hz stimulation and a stimulation–test interval of 10 min, we established the current-attack latency function in a group of 8 hamsters by stimulating them at 0, 50, 75, and 100 μA in counterbalanced order.

Results

As shown in Figure 1C, mean attack latency fell monotonically as current rose up to 100 μA. This effect was apparent, even considered individually (i.e., regressions of attack latency on current yielded a negative slope for each of the 8 subjects. Considered collectively, the reduction was statistically significant according to a repeated measures analysis of variance of log-transformed latencies, $F(3, 21) = 3.2$, $p < .05$; a post hoc orthogonal contrast of attack latency without stimulation to the mean latency following stimulation was also significant, $F(1, 21) = 6.9$, $p < .02$.

Experiment 4: Effects of CMA Stimulation on Flank Marking

Method

Does CMA stimulation just facilitate the motor patterns of attack, or does it have a more general effect on agonistic behaviors? Flank marking is a species-typical behavior of hamsters, most typically shown during agonistic encounters (e.g., Ferris, Axelson, Shinto, & Albers, 1987). To test the effects of CMA stimulation on flank marking, the subject was first stimulated or given a cable connection control. Stimulation was carried out using each subject's optimal parameters. It was transferred 10 min later from its home cage to a cage from which several group-housed intruders had just been removed. A flank mark was recorded when the subject arched its back and rubbed against the side of the soiled cage or rolled in the corner (Ferris et al., 1987). The order of tests with and without stimulation was counterbalanced across subjects.

Results

We compared the elapsed time (latency) to the first flank mark and the total number of flank marks in 10 min following stimulation and cable connection control. As shown in Table 1, CMA stimulation facilitated flank marking, producing a greater than twofold increase in the total number of marks, $t(8) = 3.0$, $p < .02$. It also produced a 30% reduction in the latency-to-flank mark, but this effect was not statistically significant, $t(8) = 1.8$.

Table 1
Effects of CMA Stimulation on Flank Marking, Locomotion, Copulation, and c-fos *Expression*

Experiment		*n*	Mean SI	Control	Stimulated
4	Flank mark latency (in s)	9	0.48	499 ± 60	347 ± 73
	Flank mark no.	—	—	1.6 ± 0.6	3.6 ± 1.1
5	Locomotor activity counts	9	0.35	1,354 ± 30	1,324 ± 36
6	Copulation latency (in s)	8	0.34	205 ± 65	201 ± 62
1–6	Fos immunoreactive nuclei/mm^2 in anterior medial nucleus (AL1 + AL2)	10	0.39	319 ± 88	644 ± 128

Note. Data in this table are means ± SEM. CMA = corticomedial amygdala; SI = stimulation index; AL = amygdala level.

Experiment 5: Effects of CMA Stimulation on Locomotion

Method

One alternative explanation for electrical attack priming is that the stimulation increases locomotor activity; such increased activity could facilitate attack by bringing subjects into contact with intruders sooner and more frequently. Such an increase might also account for the greater flank marking in Experiment 4. This hypothesis was tested by comparing the activity of 9 subjects after stimulation to that following a no-stimulation, cable connection control. Ten minutes after the stimulation or the cable connection control, the subject was transferred in its cage to the recording platform of a Columbus Instruments (Columbus, OH) activity meter in an adjacent room where it remained for 10 min. The sensitivity of the instrument was adjusted to detect gross activity but not grooming movements. The order of tests with and without stimulation was counterbalanced across subjects.

Results

Stimulation had no systematic effect on activity; there was less than a 3% difference between activity counts with or without preceding stimulation, $t(8) = 0.53$ (see Table 1). Furthermore, there were no significant correlations between the SI index and either the raw activity score following stimulation or the percentage change in activity score from stimulated to nonstimulated condition ($rs < .36$).

Experiment 6: Effects of CMA Stimulation on Copulation

Method

Flank marking is clearly increased by the odors of conspecifics (Johnston, 1975), and the effects of stimulation on flank marking might be due to heightened general olfactory–vomeronasal sensitivity or attention to pheromonal cues. A different explanation for electrical attack priming is that CMA stimulation generally alters social behavior toward conspecifics. These hypotheses were evaluated by testing the behavior of 9 male subjects toward a hormonally primed female hamster 10 min after stimulation at optimal electrical attack priming parameters and, in counterbalanced order, after a cable-connection–disconnection control. Ovariectomized females were prepared for the sex test with 200 μg of estradiol (i.m. in peanut oil) 48 and 24 hr before test and 0.5 mg progesterone 4 hr before testing. The latency to the first bout of mounting accompanied by pelvic thrusting was recorded using the same contact–proximity duration measure of latency that was used in aggression testing. The female was removed after this bout.

Results

Of the 9 subjects, 1 attended to but failed to copulate with the female in its control trial; this hamster attacked the female after CMA stimulation. The remaining 8 subjects copulated with the female on both trials. There were no systematic differences in their latencies to mount and thrust on stimulation and control trials, $t(7) = 0.04$ (see Table 1).

Electrophysiological and Neuroanatomical Results (Experiments 1–6)

Motoric and electrographic seizure activity. Kindling of seizure activity is an obvious concern in stimulation studies of the amygdala. Limiting current to ≤ 125 μA appeared to have reduced the incidence of kindling. Of the 63 hamsters implanted and tested at least once, 1 had a frank seizure on its first stimulation trial and 4 showed stimulation-related movements by their second or third trial; these hamsters were not stimulated again. Three other hamsters were removed from the study when stimulation-related movements first appeared after several weeks of testing; data from their ongoing trial set were not used.

Noise introduced by movement of the cable was a problem in the recording in a number of subjects. Technically adequate pre and poststimulation recordings were obtained from the amygdala of 13 subjects at various stages of the experiment. Of these subjects, 10 had positive SI values (mean SI = 0.26), the other 3 had negative values (mean SI = −0.45). There were no afterdischarges or seizure activity in recordings from any of these subjects.

Histological localization of electrode tip position and Fos immunocytochemistry. In 5 cases it was clear that the electrode reached the CMA, but precise localization of the tip was impossible because of tearing of the tissue during histological preparation. In these cases no attempt was made to map the tip site. Mapping was done on standard drawings relative to major white matter landmarks (e.g., mediolateral position was determined by the relative position of the tip along a horizontal line drawn between the edge of the external capsule and the ventromedial border of the optic tract). The distribution of SIs within the temporal lobe is shown in Figure 2 for 53 subjects. In the anterior amygdaloid area (AAA), there is only one highly effective locus but three of the five strongly inhibitory loci. At the two rostral levels of the amygdala (AL1 and AL2), the most effective (highest SI) tips lie ventrally; there is a tendency for the most effective loci to shift laterally as the AP plane moves posteriorly. Effective loci are highly clustered at AL2 dorsal to the anterior cortical nucleus and laterally adjacent to the medial nucleus. At more posterior levels, the highly effective loci are diffusely distributed in proximity to CMA nuclei. There was a trend for SI to increase in the anterior to posterior direction (e.g., the mean SIs ± SEMs for AAA and AL4 were

-0.03 ± 0.12 and $0.21 \pm .07$, respectively). However, the correlation between SI and AP plane, $r = .24$, did not reach conventional levels of statistical significance, $p = .09$.

Data sufficient for comparisons of the two polarity configurations were available for 27 subjects. There was a trend for the cathode ventral configuration to become the more effective one as electrode position moved anterior to posterior. This trend was clearest at AL2 and AL3. It has been claimed that, because of hyperpolarization at the anode, bipolar stimulation is most likely to produce orthodromic activation when the cathode is distal (Szabo, Nad, & Szabo, 1972; Yeomans, 1990, pp. 135–137; but see Potegal, Blau, & Miller, 1980). If our results reflect orthodromic stimulation of fibers in the stria terminalis, we may have been stimulating descending (ventrally directed) fibers terminating in the CMA.

In evaluating regional Fos immunoreactivity, we found that the size of the electrode track and the variability of its position in different subjects precluded systematic comparisons for loci other than the medial nucleus of the amygdala. Two important findings did emerge from our analysis of medial nucleus *c-fos* expression. To make the comparison of brain sections valid, we were able to identify 5 pairs of subjects that met the following criteria: (a) Their SI scores had been comparably positive; (b) their electrode tips were found to lie in the same Anterior-Posterior plane, within 1 mm of each other; and (c) one member of the pair had been stimulated before overdosing, the other had been given a cable connection control. In these pairs, stimulation was associated with a twofold increase in Fos immunoreactive nuclei over all levels; this effect was significant in the two most anterior levels of the medial nucleus, $t(4) = 3.1$, $p < .04$ (see Table 1). We were able to identify only two matched pairs of subjects with negative SI scores (i.e., hamsters in which stimulation failed to facilitate attack). In one of these pairs, the number of Fos immunoreactive nuclei was greater in the stimulated animal; in the other pair, it was less. Although these latter results are in the correct direction, more pairs would be needed to complete the demonstration that a lack of facilitation is associated with a net lack of increase in *c-fos* expression.

The second finding was that over all 11 stimulated hamsters (mean SI = 0.34), there was less than a 3% difference in total number of immunoreactive neuronal nuclei at all four levels of

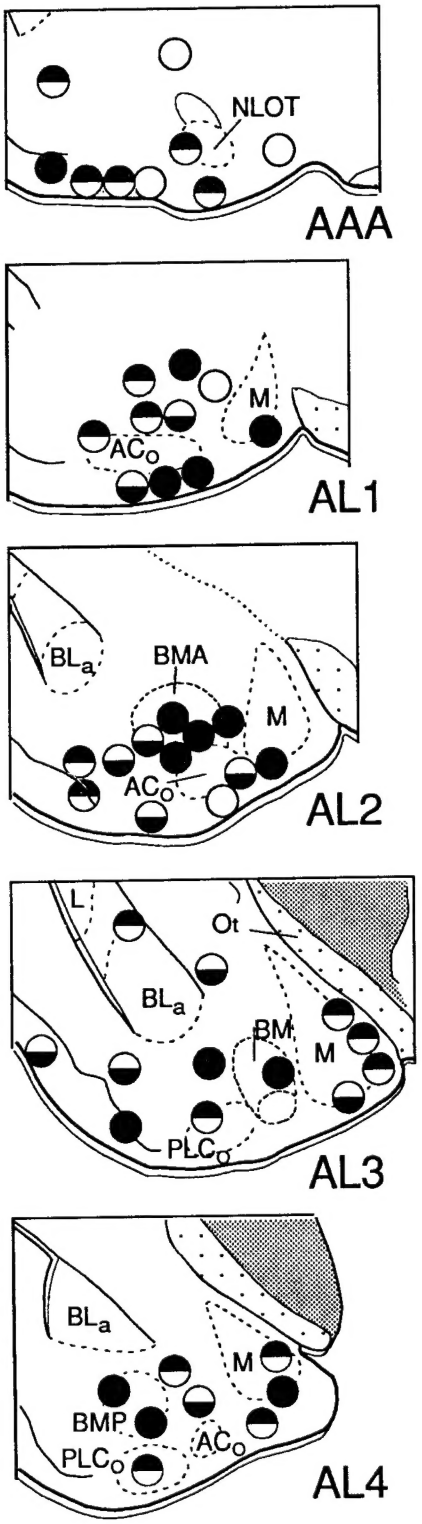

Figure 2. Tip sites of 53 electrodes that could be unambiguously localized. For three of these sites, the stimulation index (SI) value is based on one pair of stimulated and nonstimulated trials; for the remainder, SI values are the mean of two pairs of such trials. Trisecting the range of SI values, filled circles represent sites for which $1.0 > SI \geq 0.33$ (i.e., reductions in attack latency of 50% or greater), half-filled circles represent $0.33 > SI > -0.33$, and empty circles represent $-0.33 \geq SI > -1.0$ (i.e., increases in attack latency of twofold or greater). The range around 0.0 is further subdivided by top-half filling for $0.33 > SI \geq 0.0$ and bottom-half filling for $0.0 > SI \geq -0.33$. The nuclei of the corticomedial amygdala (CMA) were drawn in on our standardized maps; thus, their position relative to individual tips is only approximate, inasmuch as tips were localized relative to white matter landmarks. AAA = anterior amygdaloid area; AL1 = amygdala level 1; AL2 = amygdala level 2; AL3 = amygdala level 3; AL4 = amygdala level 4; AC_o = anterior cortical nucleus; Bl_a = anterior basolateral nucleus; BM = basomedial nucleus; BMA = anterior basomedial nucleus; BMP = posterior basomedial nucleus; L = lateral nucleus; M = medial nucleus; NLOT = nucleus of the lateral olfactory tract; Ot = optic tract; PLC_o = posterolateral cortical nucleus; sparse stipple = optic chiasm or tract; dense stipple = internal capsule.

the medial nucleus ipsilateral and contralateral to the electrode (mean ± SEM for ipsilateral medial nucleus = 294 ± 34 nuclei/mm^2; for contralateral = 288 ± 46 nuclei/mm^2). This suggests that the effects of the unilateral stimulation were distributed bilaterally. Fiber connections from the stimulated CMA to the contralateral CMA, including the commissural component of the stria terminalis (de Olmos, 1972) and the well-established projections through both ipsilateral and contralateral VMH to the CMA of the opposite side (e.g., Ono, Luiten, Nishijo, Fukuda, & Nishimo, 1985; Ottersen, 1980; Veening, 1978), may have mediated this spread of effects.

General Discussion

Specificity and Generality of Effects

The effects on agonistic behavior of high-frequency stimulation of the CMA are specific in several respects. The systematic absence of electrographic seizures in hamsters showing either positive or negative SI indices indicates that seizure activity can account for neither the facilitation nor the inhibition of aggression following CMA stimulation. Experiment 5 showed that stimulation of the CMA, which significantly reduced attack latency, did not affect locomotor activity, thus ruling out the possibility that electrical attack priming results from increased general motor activity. The validity of this test could be challenged because the subject was transferred out of the stimulation chamber in its home cage for the locomotor evaluation, whereas stimulation effects on aggression were tested within the chamber. However, stimulation effects persisted in the flank-marking test, in which the transfer was even more disruptive, inasmuch as subjects were removed from both stimulation chamber and home cage. No gross differences were noted in the topography of the attacks on stimulated versus control trials, although the possibility that stimulation subtly alters attack topography remains to be examined in detail (cf. Berntson, Hughes, & Beattie, 1976).

Experiment 6 showed that sexual behavior was also not affected by CMA stimulation. Thus, stimulation cannot act by just increasing general reactivity to olfactory–pheromonal cues. Sexual behavior resembles aggression in that the subject must orient toward and track the intruder, identify its gender, and execute the appropriate movement pattern. CMA stimulation is unlikely to be influencing these functions. Also eliminated is the possibility that CMA stimulation generates a nonspecific arousal that can be directed into any specific behaviors by available cues. We conjecture that CMA stimulation activates an aggression-specific arousal (i.e., processes that control the immediate probability of attack and associated behaviors). The lack of effect of CMA stimulation on copulation, and the implied separability of aggressive and sexual priming effects, is consistent with our purely behavioral finding that allowing male hamsters to carry out an attack on a male intruder has no systematic effect on their latency to copulate with a subsequently presented female intruder (Potegal et al., 1996). There are, however, several caveats to our conjecture. First, these hamsters were well practiced in aggression as adults but did not have any experience with females prior to the sex test, at least after arriving at the laboratory. It would be of interest to repeat these observations with hamsters having equal sexual and aggressive experience. Second, the specificity observed may be a function of the particular sites of stimulation within the CMA; stimulation of the dorsal aspect of the medial nucleus or more posterior regions near the amygdalo–hippocampal area, which contain neurons accumulating gonadal steroids and which are clearly involved in the control of sexual behavior, might have different effects.

Another potential challenge to specificity is that brain stimulation can be reinforcing. Comparing aggression associated with the onset of stimulation at certain brain loci to that associated with the offset of stimulation at other loci, Hutchinson and Renfrew (1978) argued that the attack-eliciting feature of stimulation at the former sites was that its onset was aversive, whereas attack was elicited at the latter loci because rewarding stimulation was withdrawn. In general, the aversive or rewarding properties of brain stimulation may account for some, but by no means all, instances of brain-stimulated aggression (Potegal, 1979). In the specific case of the effects reported here, the long delay between stimulation and the peak effects on aggression rules out any interpretation in terms of the reinforcing value of stimulation onset or offset.

These data also show some generality. The increase in flank marking shows that CMA stimulation effects are not limited to motor patterns of aggression but include the facilitation of other aggression-related behaviors. The flank-marking data also show that CMA stimulation can influence aspects of a behavior other than its latency. The results reported here with male hamsters fit well with our prior observations in female hamsters that the increased *c-fos* expression that follows behavioral-attack priming is restricted to the corticomedial nuclei of the amygdala and that CMA lesions in these hamsters reduce aggression without affecting locomotor activity (Potegal et al., 1991, in press). The convergence of these lines of evidence strengthens the hypothesis that the aggressive arousal mediated by the CMA is relatively specific and also suggests that, in this species, sex differences in the role of the CMA in aggressive arousal may be minimal.

Neuroanatomical Distribution of Electrode Tip Sites and Neural Models of Aggressive Arousal

Because the threshold for activating neuronal perikaryia is at least 10 times that for fibers, brain stimulation through indwelling electrodes is usually thought to involve activation of fibers (e.g., Yeomans, 1990, p. 39). At AL1 in Figure 2, the three most effective tip sites lie along the ventral surface of the brain. Ventrally running fibers in this region include lateral olfactory tract afferents to the CMA and efferents from the posterolateral and posteromedial cortical nuclei to the anterior olfactory nucleus and accessory olfactory bulb, respectively (Kevetter & Winans, 1981a, 1981b). At the three more posterior levels, where the most effective sites lie above the ventral surface, the obvious candidates are the ventral amygdalofugal pathway (VAF) and the stria terminalis (ST). However, these tracts lie at some distance from the stimulated sites. From the recommended approximation of current-distance relations, it can be calculated that stimulation at 100 and 125 μA would affect large fibers within 1.0 and 1.1 mm of the electrode tips, respectively (the effective distance is less for

finer fibers). Thus, almost all of the electrodes could have stimulated some of these fibers before or after they collect in their respective compact bundles. The densest cluster of effective sites lies in AP plane AL2, roughly equidistant from the caudal aspect of the VAF and the rostral aspect of the ST (cf. Gomez & Newman, 1992, Figure 4I–K and Figure 12E–F). Which fiber tract is most likely to be involved in electrical attack priming? The anterior–posterior gradient in SI suggests that posterior stimulation facilitates aggression more than does anterior stimulation. Furthermore, the orientation of ST fibers is more closely aligned with the dorsal–ventral polarity configurations of the electrode tips than are VAF fibers. Longitudinal stimulation of fibers is claimed to be more effective than transverse stimulation (Szabo et al., 1972; Yeomans, 1990, pp. 135–137; but see Potegal, Blau, & Miller, 1980).

The ST projects to the ventrolateral aspect of VMH and to the ventral premammillary nucleus (Gomez & Newman, 1992), regions that have been implicated in rodent aggression (Kruk, 1991). The same electrical stimulation of the hypothalamus that induced a predatory attack in cats was also found to activate an otherwise latent biting reflex in response to a touch on the cat's lips (MacDonnell & Flynn, 1966). Hypothalamically gated perioral responsiveness has also been reported in rats (D. Smith, 1972). Similarly, stimulation-dependent effects occur in the eye movements that cats use for tracking prey and in the forelimb cutaneous sensory fields that trigger their paw strikes (for review, see Kruk, 1991). The possibility that, under normal conditions, the CMA input to hypothalamus may be the drive or modulator of such state-dependent sensorimotor functions is consistent with the finding that stimulation of the more medial amygdaloid nuclei facilitates hypothalamically elicited attack (e.g., Block, Siegel, & Edinger, 1980).

As noted above, the current findings are consistent with the possibility that events associated with *c-fos* expression mediate the effects of stimulation. Thus, behavioral and electrical priming may both operate by activating CMA neurons. In a quantitative neurobehavioral model currently being developed, we propose that as each CMA neuron becomes activated by olfactory/vomeronasal cues from the intruder, it adds its increment to the instantaneous probability of attack by augmenting the activity of hypothalamically gated, attack-relevant reflexes (Potegal & Coombes, 1996). Once having been activated by exposure to the intruder on the priming trial, CMA neurons become reactivated more rapidly on the next trial, thus accounting for behavioral priming effects. In the present study, the interpretation of the inverse relationship between current and attack latency as the consequence of progressively more CMA fibers being stimulated with increasing current is consistent with the hypothesis that each activated CMA neuron adds a fractional increment to aggressive arousal. More detailed correlations of *c-fos* expression and stimulation effects across subjects are required to test these hypotheses.

Time Course of Electrical Attack Priming and LTP-Like Processes

As mentioned earlier, most authors have reported incidentally that aggressive behavior elicited from hypothalamus or periaqueductal gray rarely or never outlasts the stimulation. In formal studies, the half life of poststimulation facilitation of attack has been on the order of 10 s (Sledjeski & Flynn, 1972; Kruk et al., 1981). In contrast, persistence of effects is a motif of amygdala function. In behaving cats, activity in amygdala neurons triggered by specific stimuli persists for tens of seconds following termination of the stimulus (O'Keefe & Bouma, 1969). The poststimulation persistence of electrical priming of the CMA is consistent with the hypothesis that CMA activity prolongs aggressive arousal. Because the amygdala exerts its effects on aggression by acting through hypothalamic and brainstem mechanisms, the greater persistence of aggressive behavior following amygdala stimulation may be the consequence of activating this larger mass of neural tissue. Alternatively, the same intrinsic circuitry characteristics that render the amygdala highly susceptible to seizure disorders may, in the course of normal, nonpathological function, account for its persistence of activity.

Aggressive arousal may well depend on several neural processes partially overlapping in time. For example, Payne, Andrews, & Wilson (1984) reported a nadir in the serotonin concentration in hamster hypothalamus 30 min after a fight. The immunocytochemical evidence generated in this and in our earlier study (Potegal et al., 1991, in press) indicates that at least one of the processes in attack priming may involve the genomic modulation of neural events. Several lines of evidence suggest that a process akin to LTP may be another contributor to the time course of aggressive arousal. By design, the brief high-frequency stimulation that elicits electrical attack priming resembles that which induces LTP. LTP has been demonstrated within synapses intrinsic to the amygdala (Adamec, 1993; Chapman & Bellavance, 1992; Chapman, Kairiss, Keenan, & Brown, 1990; Clugnet & LeDoux, 1990) and in amygdalofugal pathways where it has been shown to have behavioral consequences (Adamec, 1993; Henke, 1990; Racine et al., 1983; Uno & Ozawa, 1991). Forms or components of LTP that, like electrical attack priming, achieve full development only 5–15 min after tetanization have been described in slices of rat medial amygdala in vitro (Gean, Fang-Chia, Huang, Lin, & Way, 1993; Shindou, Watanabe, Yamamoto, & Nakanishi, 1993). A slowly developing, frequency-dependent LTP has also been reported in hippocampal CA1 area; the frequency used for eliciting it was 200 Hz (Grover & Teyler 1990, 1992). The duration of electrical attack priming is roughly consistent with time constants of the LTP1 component measured by in vivo field potentials (Racine et al., 1983), although these measurements were made along amygdalo–hippocampal pathways rather than the amygdalo–hypothalamic pathways that are more likely to be involved in electrical attack priming. LTP has been reported following stimulation of both amygdala input and output pathways, including the ST (Shindou et al., 1993). In parallel with our findings, Adamec (1993) has reported that unilateral stimulation induced bilateral LTP in amygdalofugal pathways. Shindou et al. (1993, Figure 5, p. 671) found an increase in excitatory post synaptic potential slope to single pulse (0.1 Hz) stimulation in medial amygdala neurons in vitro that peaked 10–15 min after tetanization through the ST. Preloading neurons with a CA^{++}-chelator revealed that tetanization initiated at least two separate but partially overlapping processes: a more rapid CA^{++} independent process and a

slower CA^{++} dependent process. Finally, Abraham et al. (1993) reported that the induction of LTP in the dentate of awake rats by high-frequency stimulation is associated with the local expression of early intermediate genes, including *c-fos*.

The consistency in Experiment 1 of finding a nadir at 200 Hz in both stimulation frequency-attack latency functions is noteworthy given the difference in the other stimulation parameters used in establishing the two functions. This unanticipated frequency specificity suggests that the CMA circuitry may in some way be tuned to a frequency near 200 Hz. This frequency has been found optimal for stimulation of *N*-methyl-D-aspartate receptor-mediated potentials in in vitro amygdala slices (Nakanishi et al., 1990). Bursts of 200-Hz oscillations have been recorded in vivo in CA1 hippocampal interneurons during the performance of certain behaviors (Buzsáki, Horváth, Urioste, Hetke, & Wise, 1992). Thus, stimulation at this frequency might entrain behavior-relevant oscillations or otherwise induce a maximal change in synaptic function. Taken together, the foregoing evidence is consistent with the possibility that electrical attack priming is a nonassociative, decremental form of LTP; evaluating this possibility would involve determining if the physiological changes are synaptic and, if so, identifying the locus of these synapses.

Cross-Species Generality

What might be the generality of these results across species? The time course of behaviorally induced attack priming effects in rats and hamsters is quite similar (Potegal, 1992); a preliminary study of the effects of priming on CMA *c-fos* expression suggests that similar increases occur in rats (Potegal et al., 1991). However, rodent aggression is heavily dependent on pheromonal cues transduced by olfactory/vomeronasal input; the CMA is the amygdala's receiving area for this input. The possibility that the medial amygdala is important in mediating social interactions in microsomatic species whose behavior is less strongly controlled by olfactory/vomeronasal stimuli is suggested by the observation that medial amygdaloid neurons in rhesus macaques are responsive to the facial expressions of other monkeys (e.g., Brothers, Ring, & Kling, 1990; Rolls, 1984).

For humans, the claim that rage attacks in individuals with temporal lobe epilepsy are associated with amygdaloid seizure activity or interictal phenomena is both well-known and controversial (e.g., J. S. Smith, 1980; for review, see Potegal, 1994). In observations complementary to those of Fuller et al. (1957) and Shipley and Kolb (1977) in dogs and hamsters, respectively, Lewis, Pincus, Shanok, and Glaser (1982) noted that individuals with psychomotor epilepsy claim that once they have begun to fight, they are unable to stop. Against the background of CMA stimulation effects reported here, we find noteworthy two case reports of patients who showed delayed and prolonged outbursts of aggression following stimulation through chronic electrodes that had been implanted in the amygdala in preparation for surgical treatment of temporal lobe epilepsy (Ervin, Mark, & Stevens, 1969; Stevens, Mark, Ervin, Pacheco, & Suenatsu, 1969). One of us has speculated that humans may experience aggressive arousal as felt anger, the persistence of which is the same order of magnitude as the priming effect in rodents (Potegal, 1994). Most generally, these results suggest the possibility that transient emotional states including, but perhaps not limited to, anger may be mediated by LTP-like processes that heretofore have been the speculative province of learning and memory.

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